REMARKS

Applicants acknowledge with appreciation the Examiner's statement that claims 19-30, which are *in silico* screening methods, have practical application, and thus are statutory and have utility under 35 U.S.C. §§ 101 and 112.

Applicants have amended claims 19-23 to improve their form and for clarity. Support for these amendments appears, e.g., in claims 19-23 as originally filed.

Applicants have added claims 31-34 directed to methods for evaluating the binding of a compound or identifying a compound capable of associating with a CnA/CnB molecule or molecular complex comprising the steps of producing a crystal of a CnA/CnB molecule or molecular complex, determining its three-dimensional structure and identifying its binding pocket. Support for these claims can be found in the application as originally filed, particularly, for example, on pg. 4, lines 4-16; pg. 27, lines 11-29; pg. 30, line 13 to pg. 32, line 25; and pg. 35, line 16 to pg. 36, line 2 of the application as originally filed.

None of these amendments adds new matter.

The Rejections

35 U.S.C. § 103

Claims 19-25 stand rejected under 35 U.S.C. § 103(a) as obvious in view of United States Patent No. 5,705,335 (hereinafter "Hendry"). Specifically, the Examiner contends that Hendry teaches a method to evaluate the ability of a chemical compound to associate with another molecule (in particular, the "degree of fit" of binding to a pharmacophore) wherein a ligand is docked (fitting operation) into a binding site, and the results evaluated. Additionally, the Examiner alleges that Hendry teaches "outputting" results of this fitting method, the synthesis of compounds identified by using a computer modeling/docking algorithm and subsequent evaluation by means of *in vitro* assays. The Examiner therefore contends that due to all of these purported teachings, Hendry renders obvious the claims of the instant application.

Citing *In re Gulack*, MPEP 2106 and the Trilateral Project WM4 Report, the Examiner contends that the structure coordinates recited in the claims are nonfunctional

descriptive material insofar as they do not impose a change upon the processing steps used in the claimed methods. The Examiner alleges that algorithms to fit or dock a molecular entity into the binding site of a molecule or molecular complex are known in the art. The Examiner asserts that the instant claims are not made nonobvious because of their use with new calcineurin structural coordinate data since non-functional descriptive material cannot render non-obvious an invention that would have otherwise been obvious. Applicants traverse.

Contrary to the assertion of the Examiner, the novel structure coordinates of calcineurin do impose a change on the processing steps in the claimed methods. Further, the structure coordinates of the molecule or molecular complex affect the manner in which the computer containing the coordinates functions. The structure coordinates provide the parameters, metes and bounds within which the fitting operation is performed and therefore dictate the computer programs themselves. For example, the spatial relationship of the atoms established in the structure coordinates of the molecule or molecular complex determines the manner in which the docking program probes the surface of the molecule or molecular complex for shape complementarity or a particular energetically favorable, electrostatic or Van der Waals interaction in relation to the chemical entity. As a further example, the unique energy surface provided by the structure coordinates of the molecule or molecular complex dictates the cycle in which the energy minimization algorithm searches for local energy minima in pursuit of the global energy minimum. For example, the spatial relationship of the atoms set forth by the structure coordinates of the molecule or molecular complex determine how the molecular dynamics algorithm will integrate forces applied to the molecule or molecular complex and the chemical entity. Therefore, the structure coordinates of the molecule or molecular complex determine how the process steps of the claimed method are performed, and in so doing, alters how the computer upon which these calculations are performed functions.

Applicants direct the Examiner to the definition of "functional descriptive material" in MPEP 2106 IV. B. 1.:

"[F]unctional descriptive material consists of data structures and computer programs which impart **functionality** when employed as a computer component. (The

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definition of "data structure" is "a physical or logical relationship among data elements, designed to support specific data manipulation functions."" (emphasis added, citation omitted)
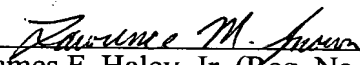
There is indeed a spatial/physical relationship between the structure coordinates of each atom in the molecule or molecular complex. This spatial/physical relationship determines how the computer program for drug discovery and computer functions. Further, the structure coordinates of the molecule or molecular complex impart functionality by producing a practical application, for example, providing a useful compound that specifically associates with the molecule or molecular complex comprising the CnA or CnB binding pocket or homologue thereof, a utility recognized by the Examiner. The structure coordinates are not analogous to printed matter with no actual function, such as music or literary works. Therefore, the structure coordinates of the molecule or molecular complex are functional descriptive material, and should be accorded patentable weight.

In addition, Hendry does not teach or suggest using the structure coordinates from calcineurin A or B or a homologue thereof in combination with a method involving a fitting operation. Furthermore, as in claims 19, 20, 21, 25, 26 and 27 and the claims dependent therefrom, the starting material is a new and unobvious set of structure coordinates from calcineurin or a homologue thereof, and the resulting materials and methods are new, unobvious and unpredicted: a chemical entity that specifically associates with the molecule or molecular complex comprising the CnA or CnB binding pocket. Therefore, claims 19-34 are not obvious in view of Hendry. In view of the above arguments, applicants request the withdrawal of the rejection under 35 U.S.C. § 103.

Conclusion

Applicants request that the Examiner enter the above amendments, consider the foregoing remarks and allow the pending claims to issue. If the Examiner believes that a telephonic interview would be helpful, she is invited to call applicants' attorney or agents at any time.

Respectfully submitted,

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APPENDIX OF AMENDMENTS

We claim:

19.   (Five Times Amended) A method of using a computer for evaluating the ability of at least one of a plurality of chemical entities to associate with a [crystallized] molecule or molecular complex comprising a calcineurin A (CnA) binding pocket defined by structure coordinates of CnA amino acids 90, 91, 92, 118, 120, 121, 122, 150, 151, 156, 160, 199, 232, 253, 254, 256, 281, 282, 283, 284, 306, 311, 312, and 317 according to Figure 1, or a homologue of said molecule or molecular complex wherein said homologue comprises a CnA homologue binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å;
wherein said computer comprises a machine-readable data storage medium comprising a data storage material encoded with said structure coordinates defining said binding pocket and wherein said method comprises the steps of: .
          a)   [positioning a graphical three-dimensional representation of the structure of] utilizing said structure coordinates defining said binding pocket and the structure coordinates of one of said plurality of chemical entities to position a chemical entity within the CnA binding pocket or the CnA homologue binding pocket;
          b)   performing a fitting operation between [said graphical representation of the structure of] said chemical entity and the CnA binding pocket or the CnA homologue binding pocket by employing computational means which utilize said [graphical representation of the structure

and said] structure coordinates <u>of the binding pocket or the</u>
<u>chemical entity</u> ;

    c) analyzing the results of said fitting
operation to quantify the association between said chemical
entity and the CnA binding pocket or the CnA homologue
binding pocket;

    [d) outputting said quantified association
to a suitable output hardware;]

    [e)] <u>d)</u> optionally repeating steps a)
through [d)] <u>c)</u> with another of said plurality of chemical
entities; and

    [f)] <u>e)</u> selecting at least one of said
plurality of chemical entities that associates with the CnA
binding pocket or the CnA homologue binding pocket based on
said quantified association of said chemical entity.

  20. (Five Times Amended) A method of using a
computer for evaluating the ability of at least one of a
plurality of chemical entities to associate with a
[crystallized] molecule or molecular complex comprising a CnA
binding pocket defined by structure coordinates of CnA amino
acids 90, 91, 92, 118, 120, 121, 122, 150, 151, 156, 160,
199, 281, 282, 283, 306, 311, 232, and 254, according to
Figure 1, or a homologue of said molecule or molecular
complex, wherein said homologue comprises a CnA homologue
binding pocket that has a root mean square deviation from the
backbone atoms of said amino acids of not more than 1.5Å;
wherein said computer comprises a machine-readable data
storage medium comprising a data storage material encoded
with said structure coordinates defining said binding pocket
and wherein said method comprises the steps of:

a)   [positioning a graphical three-dimensional representation of the structure of] <u>utilizing said structure coordinates defining said binding pocket and the structure coordinates of</u> one of said plurality of chemical entities <u>to position a chemical entity</u> within the CnA binding pocket or the CnA homologue binding pocket;

b)   performing a fitting operation between [said graphical representation of the structure of] said chemical entity and the CnA binding pocket or the CnA homologue binding pocket by employing computational means which utilize said [graphical representation of the structure and said] structure coordinates <u>of the binding pocket or the chemical entity</u> ;

c)   analyzing the results of said fitting operation to quantify the association between said chemical entity and the CnA binding pocket or the CnA homologue binding pocket;

[d)   outputting said quantified association to a suitable output hardware;]

[e)] <u>d)</u>   optionally repeating steps a) through [d)] <u>c)</u> with another of said plurality of chemical entities; and

[f)] <u>e)</u>   selecting at least one of said plurality of chemical entities that associates with the CnA binding pocket or the CnA homologue binding pocket based on said quantified association of said chemical entity.

21.   (Five Times Amended) A method of using a computer for evaluating the ability of at least one of a plurality of chemical entities to associate with a [crystallized] molecule or molecular complex comprising a CnA/CnB binding pocket defined by structure coordinates of

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CnA amino acids 122, 124, 159, 160, 310, 312, 313, 314, 339, 341, 343, 344, 345, 347, 351, 352, 353, 354, 355, 356, 359, 360, and 363; and calcineurin B (CnB) amino acids 49, 50, 114, 115, 118, 119, 121, 122, 123, 124, 157, 158, 159, 161, and 162 according to Figure 1, or a homologue of said molecule or molecular complex, wherein said homologue comprises a CnA/CnB homologue binding pocket that has a root mean square deviation from the backbone atoms of said CnA and CnB amino acids of not more than 1.5Å; wherein said computer comprises a machine-readable data storage medium comprising a data storage material encoded with said structure coordinates defining said binding pocket and wherein said method comprises the steps of:

a)   [positioning a graphical three-dimensional representation of the structure of] <u>utilizing said structure coordinates defining said binding pocket and the structure coordinates of</u> one of said plurality of chemical entities <u>to position a chemical entity</u> within the CnA/CnB binding pocket or the CnA/CnB homologue binding pocket;

b)   performing a fitting operation between [said graphical representation of the structure of] said chemical entity and the CnA/CnB binding pocket or the CnA/CnB homologue binding pocket by employing computational means which utilize said [graphical representation of the structure and said] structure coordinates <u>of the binding pocket or the chemical entity</u>;

c)   analyzing the results of said fitting operation to quantify the association between said chemical entity and the CnA/CnB binding pocket or the CnA/CnB homologue binding pocket;

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[d) outputting said quantified association to a suitable output hardware;]

[e)] d) optionally repeating steps a) through [d)] c) with another of said plurality of chemical entities; and

[f)] e) selecting at least one of said plurality of chemical entities that associates with the CnA/CnB binding pocket or the CnA/CnB homologue binding pocket based on said quantified association of said chemical entity.

22. (Thrice amended) The method according to claim 19 or 20, wherein said [crystallized] molecule or molecular complex further comprises a second binding pocket defined by CnA amino acids 122, 124, 159, 160, 310, 312, 313, 314, 339, 341, 343, 344, 345, 347, 351, 352, 353, 354, 355, 356, 359, 360, and 363; and CnB amino acids 49, 50, 114, 115, 118, 119, 121, 122, 123, 124, 157, 158, 159, 161, and 162; according to Figure 1, or a homologue of said molecule or molecular complex, wherein said homologue comprises a second homologue binding pocket that has a root mean square deviation from the backbone atoms of said CnA and CnB amino acids of not more than 1.5Å.

23. (Thrice amended) The method according to claim 22, wherein said [crystallized] molecule or molecular complex is defined by the entire set of structure coordinates according to Figure 1, or a homologue thereof, wherein said homologue has a root mean square deviation from the backbone atoms of said CnA and CnB amino acids of not more than 1.5Å.

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